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DOCKET NO. : CELG-0119

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Khetani et al.

Serial No.: Not Assigned Yet

Group Art Unit: Not Assigned Yet

Filing Date: Herewith

Examiner: Not Assigned Yet

For: Processes and Intermediates for Resolving Piperidyl Acetamide Stereoisomers



EXPRESS MAIL LABEL NO: EL219294275US

DATE OF DEPOSIT: April 1, 1999

Box ☒ Patent Application
☐ Provisional ☐ Design ☐ Sequence

Assistant Commissioner for Patents
Washington DC 20231

PATENT APPLICATION TRANSMITTAL LETTER

Transmitted herewith for filing, please find

☒ A Utility Patent Application under 37 C.F.R. 1.53(b).

It is a continuing application, as follows:

☒ continuation ☐ divisional ☐ continuation-in-part of prior application number
08/861,988 filed May 22, 1997.

☐ A Provisional Patent Application under 37 C.F.R. 1.53(c).

☐ A Design Patent Application (submitted in duplicate).

Including the following:

☐ Provisional Application Cover Sheet.

09/28/95

- ☐ New or Revised Specification, including pages ___ to ___ containing:
- ☐ Specification
 - ☐ Claims
 - ☐ Abstract
 - ☐ Substitute Specification, including Claims and Abstract.
- ☐ The present application is a continuation application of Application No. _____ filed _____. The present application includes the Specification of the parent application which has been revised in accordance with the amendments filed in the parent application. Since none of those amendments incorporate new matter into the parent application, the present revised Specification also does not include new matter.
- ☐ The present application is a continuation application of Application No. _____ filed _____, which in turn is a continuation-in-part of Application No. _____ filed _____. The present application includes the Specification of the parent application which has been revised in accordance with the amendments filed in the parent application. Although the amendments in the parent C-I-P application may have incorporated new matter, since those are the only revisions included in the present application, the present application includes no new matter in relation to the parent application.
- ☒ A copy of earlier application Serial No. 08/861,988 Filed May 22, 1997, including Specification, Claims and Abstract (pages 1 - 26), to which no new matter has been added TOGETHER WITH a copy of the executed oath or declaration for such earlier application and all drawings and appendices. Such earlier application is hereby incorporated into the present application by reference.
- ☒ Please enter the following amendment to the Specification under the Cross-Reference to Related Applications section (or create such a section) : "This Application:
- ☒ is a continuation of ☐ is a divisional of ☐ claims benefit of U.S. provisional Application Serial No. 08/861,988 filed May 22, 1997.
- ☐ Signed Statement attached deleting inventor(s) named in the prior application.
- ☒ A Preliminary Amendment.
- ☐ _____ Sheets of ☐ Formal ☐ Informal Drawings.

- ☐ Petition to Accept Photographic Drawings.
- ☐ Petition Fee
- ☐ An ☐ Executed ☐ Unexecuted Declaration or Oath and Power of Attorney.
- ☐ An Associate Power of Attorney.
- ☐ An ☐ Executed ☐ Copy of Executed Assignment of the Invention to _____
- ☐ A Recordation Form Cover Sheet.
- ☐ Recordation Fee - \$40.00.
- ☒ The prior application is assigned of record to Celgene Corporation.
- ☐ Priority is claimed under 35 U.S.C. § 119 of Patent Application No. _____ filed _____ in _____ (country).
- ☐ A Certified Copy of each of the above applications for which priority is claimed:
- ☐ is enclosed.
- ☐ has been filed in prior application Serial No. _____ filed _____.
- ☒ An ☒ Executed or ☐ Copy of Earlier Statement Claiming Small Entity Status under 37 C.F.R. 1.9 and 1.27
- ☐ is enclosed.
- ☒ has been filed in prior application Serial No. 08/861,988 filed May 22, 1997, said status is still proper and desired in present case.
- ☐ Diskette Containing DNA/Amino Acid Sequence Information.
- ☐ Statement to Support Submission of DNA/Amino Acid Sequence Information.
- ☐ The computer readable form in this application _____, is identical with that filed in Application Serial Number _____, filed _____. In accordance with 37 CFR 1.821(e), please use the ☐ first-filed, ☐ last-filed or ☐ only computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application. A paper copy of the Sequence

Listing is ☐ included in the originally-filed specification of the instant application,
☐ included in a separately filed preliminary amendment for incorporation into the
specification.

- ☐ Information Disclosure Statement.
- ☐ Attached Form 1449.
- ☐ Copies of each of the references listed on the attached Form PTO-1449 are
enclosed herewith.
- ☐ A copy of Petition for Extension of Time as filed in the prior case.
- ☐ Appended Material as follows: _____ .
- ☒ Return Receipt Postcard (should be specifically itemized).
- ☐ Other as follows: _____

_____ .

FEE CALCULATION:

- ☒ Cancel in this application original claim 9 of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

| | | | SMALL ENTITY | | NOT SMALL ENTITY | |
|--|-----------|-----------|--------------|----------|------------------|-----|
| | | | RATE | FEE | RATE | FEE |
| PROVISIONAL APPLICATION | | | \$75.00 | \$ | \$150.00 | \$ |
| DESIGN APPLICATION | | | \$155.00 | \$ | \$310.00 | \$ |
| UTILITY APPLICATIONS BASE FEE | | | \$380.00 | \$380.00 | \$760.00 | \$ |
| UTILITY APPLICATION; ALL CLAIMS CALCULATED AFTER ENTRY OF ALL AMENDMENTS | | | | | | |
| | No. Filed | No. Extra | | | | |
| TOTAL CLAIMS | 13- 20 = | 0 | \$9 each | \$ | \$18 each | \$ |
| INDEP. CLAIMS | 1- 3 = | 0 | \$39 each | \$ | \$78 each | \$ |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM | | | \$130 | \$ | \$260 | \$ |
| ADDITIONAL FILING FEE | | | | \$ | | \$ |
| TOTAL FILING FEE DUE | | | | \$ | | \$ |

- ☒ A Check is enclosed in the amount of \$380.00.
- ☒ The Commissioner is authorized to charge payment of the following fees and to refund any overpayment associated with this communication or during the pendency of this application to deposit account 23-3050. This sheet is provided in duplicate.
- ☐ The foregoing amount due.
- ☒ Any additional filing fees required, including fees for the presentation of extra claims under 37 C.F.R. 1.16.
- ☒ Any additional patent application processing fees under 37 C.F.R. 1.17 or 1.20(d).
- ☐ The issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance.
- ☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit

account 23-3050. This sheet is provided in duplicate.

SHOULD ANY DEFICIENCIES APPEAR with respect to this application, including deficiencies in payment of fees, missing parts of the application or otherwise, the United States Patent and Trademark Office is respectfully requested to promptly notify the undersigned.

Date: April 1, 1999

Reuben S. Gibson 4/1/89

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For: Processes and Intermediates For Resolving Piperidyl Acetamide Stereoisomers

**Assistant Commissioner
for Patents
Washington, D.C. 20231**

PRELIMINARY AMENDMENT

Applicants request that the following amendments be entered, without prejudice, as follows:

In the specification:

Please add as the first sentence after the title --This is a continuation of Serial No. 08/861,988 filed May 22, 1997--.

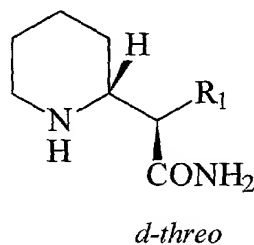
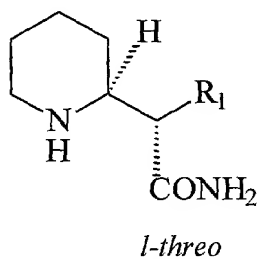
In the claims:

Please cancel claim 9.

Please amend claims 1 as follows:

1. (Amended) A synthetic process comprising the steps of preferentially forming *d-threo* acid salts of *d-threo* piperidyl acetamide stereoisomers with respect to *l-threo* piperidyl acetamide stereoisomers by:

providing a mixture of said *d,l-threo* piperidyl acetamide stereoisomers having formulas:

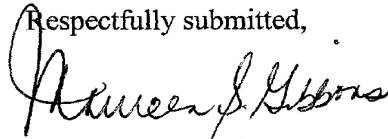


wherein R₁ is aryl having about 6 to about 28 carbon atoms; and

reacting said stereoisomers with an acid resolving agent in an organic solvent[, thereby forming acid salts of said *d-threo* stereoisomers preferentially with respect to said *l-threo* stereoisomers].

REMARKS

The present application is a continuation of application No. 08/861,988 filed May 22, 1997., which was subsequently allowed on November 10, 1998. The present claims are directed to subject matter canceled during the prosecution of application No. 08/861,988.

Respectfully submitted,

Maureen S. Gibbons
Registration No. 44,121

Date: April 1, 1999

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**PROCESSES AND INTERMEDIATES FOR RESOLVING
PIPERIDYL ACETAMIDE STEREOISOMERS**

FIELD OF THE INVENTION

This invention is directed to novel processes for resolution of piperidyl acetamide
5 stereoisomers. The invention additionally is directed to synthetic intermediates and reaction
products useful in such processes.

BACKGROUND OF THE INVENTION

Substituted piperidines have found use in the treatment of many nervous system
disorders. For example, methylphenidate has been used to treat Attention Deficit Disorder
10 (ADD), Attention Deficit Hyperactivity Disorder (ADHD) and cognitive decline in Acquired
Immunodeficiency Syndrome (AIDS) and AIDS Related Complex (ARC) patients. (*See, e.g.,*
Greenhill, Child & Adol. Psych. Clin. N.A., 1995, 4, 123, and Brown, Intl. J. Psychl. Med.,
1995, 25, 21).

Many currently available synthetic routes to methylphenidate and other substituted
15 piperidines involve preparation of racemic mixtures. (*See, e.g.,* U.S. Patent 2,507,631, to

Hartmann, *et al.*, and U.S. Patent 2,957,880, to Rometsch, *et al.*). There are, however, a number of disadvantages associated with racemic mixtures of such drugs. Current administration of racemic methylphenidate often results in notable side effects such as anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic
5 methylphenidate produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

U.S. Patent Nos. 2,507,631 and 2,957,880 disclose synthetic procedures wherein methylphenidate, alternatively known as methyl α -piperid-2-ylphenylacetate, is prepared through a multi-step process in which 2-chloropyridine and phenylacetonitrile initially are
10 coupled to form α -pyrid-2-ylphenylacetonitrile. The resulting α -pyrid-2-ylphenylacetonitrile then is hydrated in the presence of acid to yield α -pyrid-2-ylphenylacetamide which, in turn, is either: (a) catalytically hydrogenated to yield α -piperid-2-ylphenylacetamide and then converted to methyl α -piperid-2-ylphenylacetate, or (b) converted to methyl α -pyrid-2-ylphenylacetate which, in turn, is hydrogenated to yield methyl α -piperid-2-ylphenylacetate.

15 In the first embodiment of U.S. Patent No. 2,507,631 and in the process described in U.S. Patent No. 2,957,880, α -piperid-2-ylphenylacetamide is first separated into the *threo* and *erythro* diastereomeric racemates. This is accomplished through evaporation of the solvent utilized in the hydrogenation (*i.e.*, acetic acid), addition of sodium hydroxide to precipitate the α -piperid-2-ylphenylacetamide free base, recrystallization of this amide from
20 ethyl acetate, and preferential crystallization of the *erythro* form by passing gaseous hydrogen chloride through an ethanolic solution of the amide.

The isolated *erythro* racemate then is resolved through formation of the *l*-tartrate salt, repeated recrystallizations of this salt from 96% ethanol are performed until a constant rotation is obtained, and the *l-erythro* form of α -piperid-2-ylphenylacetamide is precipitated

with sodium hydroxide. The *l-erythro* form of α -piperid-2-ylphenylacetamide thus obtained is said to be subjected to epimerization to yield the desired *d-threo* diastereomer of α -piperid-2-ylphenylacetamide through treatment with 6 M potassium hydroxide. According to the disclosed procedure, the α -piperid-2-ylphenylacetamide thus obtained is converted to *d-threo* methyl α -piperid-2-ylphenylacetate through hydrolysis and esterification.

Some in the art have raised doubts as to whether the procedures disclosed in U.S. Patent Nos. 2,507,631 and 2,957,880 do, in fact, produce the desired *d-threo* isomer. Indeed, J.R. Soares, "Stereochemical Studies On Potential Central Nervous System Active Agents and Studies On The Chemistry Of Some 3-Benzoylpiperidines," 1971, Columbia University Ph.D. dissertation, p. 115, discloses that "all attempts to epimerize the resolved *erythro*-amides to the corresponding threo-amides by the procedure outlined in [U.S. 2,957,880] failed completely."

In any event, the synthetic procedure described in U.S. Patent Nos. 2,507,631 and 2,957,880 is wasteful in that it involves discarding the *threo* α -piperid-2-ylphenylacetamide racemate which is isolated following the recrystallization step and which typically represents approximately 25% of the acetamide product obtained via hydrogenation.

Consequently, there remains a need in the art for alternative synthetic procedures for the preparation of methylphenidate and other substituted piperidines. In particular, there is a need for synthetic procedures that do not require separating and discarding *threo* stereoisomers from the hydrogenation reaction product.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide processes for the preparation of substituted piperidines.

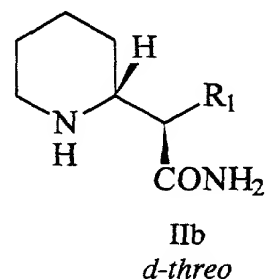
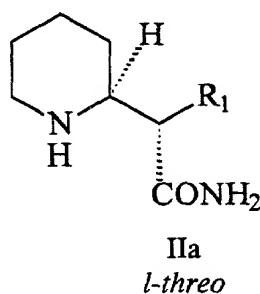
It is another object of this invention to provide processes that provide synthetic intermediates and, hence, products having high optical purity.

It is yet another object to provide processes that proceed more efficiently than the processes disclosed by the prior art.

5 SUMMARY OF THE INVENTION

These and other objects are satisfied by the present invention, which provides processes and intermediates for preparing piperidyl acetamides. In preferred embodiments, the processes of the invention comprise reacting *d,l-threo* piperidyl acetamide stereoisomers having formulas IIa and IIb:

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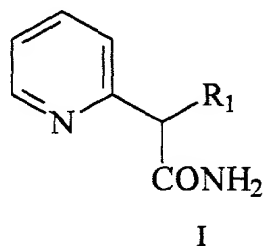


(R₁ = aryl having about 6 to about 28 carbon atoms) with an acid resolving agent in an organic solvent, thereby forming acid salts of the *d-threo* stereoisomers preferentially with respect to the *l-threo* stereoisomers. The resulting acid salts then are reacted with aqueous base to form
15 the corresponding piperidyl acetamide, which subsequently is converted to a corresponding ester.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides novel processes for stereoselective synthesis of a variety 2-substituted piperidine stereoisomers. In one aspect, the invention is directed to synthetic methods involving hydrogenation of pyridines having formula I:

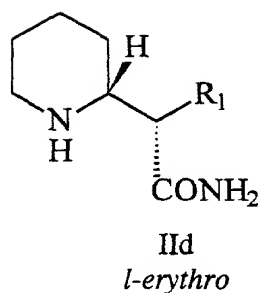
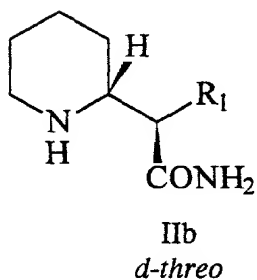
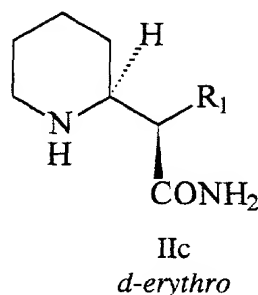
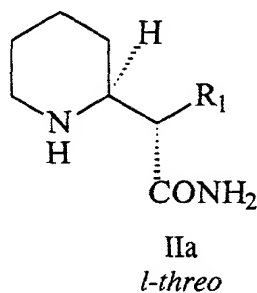
5



wherein R₁ is aryl having about 6 to about 28 carbon atoms. Aryl groups, as used herein, are aromatic groups containing a delocalized π -electron cloud. Such aromatic groups can be substituted with one or more substituents, such as, for example, halo, alkyl, aryl, hydroxy, alkoxy, carboxy, and cycloalkyl. Exemplary aryl groups include phenyl, naphthyl, xylyl, chlorophenyl, fluorophenyl, trifluoromethylphenyl, and bromophenyl. Phenyl groups are preferred.

This hydrogenation can be effected by any of the numerous techniques known in the art. One preferred hydrogenation technique involves reacting the pyridine with hydrogen gas in the presence of a suitable catalyst in an alkanolic acid having 1 to about 10 carbon atoms. The hydrogenation preferably run at 25 °C and 40 psi. Representative catalysts contain platinum, with platinum oxide being particularly preferred. One preferred alkanolic acid is acetic acid.

Hydrogenation of pyridine I provides a mixture of piperidine diastereomers IIa-d:

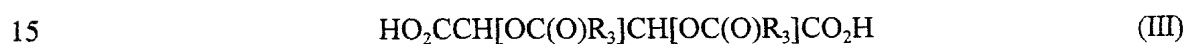


In accordance with the present invention, this mixture is treated with an organic base in an organic solvent to epimerize the *erythro* stereoisomers into *threo* forms. The epimerization can, for example, be effected in an aromatic hydrocarbon solvent such as toluene using an alkali metal alkoxide such as potassium *tert*-butoxide. In preferred embodiments, the epimerization is effected at 70 °C in an aromatic hydrocarbon solvent such as toluene using two equivalents of an alkali metal alkoxide such as potassium *tert*-butoxide.

The resulting composition, which should consist predominantly of *d,l-threo* piperidyl acetamide stereoisomers, is reacted with an acid resolving agent in an organic solvent, thereby forming acid salts of the *d-threo* stereoisomers preferentially with respect to the *l-threo* stereoisomers. Alkyl groups according to the invention are hydrocarbons which are straight, branched, or cyclic. Such hydrocarbons can be substituted with one or more substituents, such as, for example, halo, hydroxy, alkoxy, and carboxy groups. Exemplary alkyl groups

include methyl, ethyl, isopropyl, *n*-butyl, *t*-butyl, *n*-pentyl, acetyl, trifluoromethyl, chloromethyl, and hexyl groups. Representative solvents include alcohols, alkyl alkanoates (*e.g.*, ethyl acetate), ketones (*e.g.*, acetone), and ethers (*e.g.*, tetrahydrofuran, dioxane). Preferred solvents are alcohols having 1 to about 5 carbon atoms, include branched and
5 straight chain compounds such as ethyl, propyl and *tert*-butyl alcohol, with isopropanol being particularly preferred. The reaction of piperidyl acetamide stereoisomers with acid resolving agents preferably is performed with stirring at room temperature.

Representative acid resolving agents include L-(+)- or D-(-)- tartaric acid, dipivaloyl-D-tartaric acid, (1S)-(+)-10-camphorsulphonic acid, L-(-)-malic acid, (S)-(+)-
10 mandelic acid, N-acetyl-*L*-aspartic acid (and other N-protected amino acids), (R)-(+)-1,1'-bi-s-naphthol, (+)-camphoric acid, D-glucuronic acid, and derivatives thereof. Those believed to be useful for forming *d-threo* stereoisomers preferentially with respect to *l-threo* isomers include (+)-dibenzoyl-D-tartaric acid. Derivatives of D-(-)-tartaric acid are preferred, including those having formula (III):



where each R₃, independently, is aryl having 6 to about 28 carbon atoms or aralkyl having 7 to about 28 carbon atoms. Aralkyl groups according to the invention are those (such as, for example, benzyl groups, which both aryl and alkyl portions and are covalently bound to a core molecule (such as the above-noted carbonyl-functionalized tartaric acid) through the alkyl
20 portions thereof.

In certain alternative embodiments of the invention, the piperidyl acetamide stereoisomers having formulas IIa and IIb are reacted with an acid resolving agent in an organic solvent to form acid salts of the *l-threo* stereoisomers preferentially with respect to the *d-threo* stereoisomers. Resolving agents believed to be useful for forming *l-threo*

stereoisomers preferentially with respect to *d-threo* isomers include (-)-dibenzoyl-L-tartaric acid. Derivatives of L-(-)-tartaric acid are preferred, including those having formula (III). Crystallization preferably is performed at ambient temperature.

The acid salts obtained via resolution typically are dissolved in water and treated
5 with an aqueous base such as a carbonate, bicarbonate, or hydroxide to precipitate the corresponding piperidyl amide free base in substantially pure form. They then can be reacted with an alcohol having, for example, 1 to about 5 carbon atoms in the presence of acid to form the corresponding ester.

Additional objects, advantages, and novel features of this invention will become
10 apparent to those skilled in the art upon examination of the following examples thereof, which are not intended to be limiting.

Example 1

Preparation of *d-Threo*-methylphenidate Hydrochloride *Via* Diastereomeric Separation and Resolution of *d,l-erythro*-Amide (Comparative Example)

15 A. α -Phenyl- α -pyridyl-(2)-acetonitrile

Materials:

| | | |
|----|------------------------|--------------------|
| | 2-Chloropyridine (99%) | 286 g (2.50 moles) |
| | Benzyl cyanide (98%) | 314 g (2.62 moles) |
| | Sodium amide (90%) | 217 g (5.00 moles) |
| 20 | Toluene | 0.98 + 0.17 L |
| | Water | 0.87 L |
| | Ethyl acetate | 0.43 L |
| | Hexanes | 1.56 + 1.95 L |
| 25 | Brine | 0.43 L |

Procedure:

A 5L multi-neck glass reactor was charged with 2-chloropyridine, benzyl cyanide, and toluene (0.98 L). Sodium amide powder was added over a 1h period via a solid-addition funnel, keeping the reaction temperature below 30°C. The reaction mixture was stirred for 5 16h at ambient temperature. The reaction was then cooled to ~ 10°C, and quenched with 0.87 L water. Ethyl acetate (0.43 L) was added to solubilize the precipitated product. The organic layer was separated and washed once with 0.43 L brine. Solvent was removed from the organic layer on a rotovap, and toluene (0.17L), followed by hexanes (1.56 L), were added to the resulting residue. The resulting slurry was filtered. The filter cake was washed 10 with hexanes (1.95 L), and dried to give 441 g of α -phenyl- α -pyridyl-(2)-acetonitrile as light brown crystals (90% yield based on 2-chloropyridine).

B. α -Phenyl- α -pyridyl-(2)-acetamide

Materials:

| | | |
|----|--|--------------------|
| | α -Phenyl- α -pyridyl-(2)-acetonitrile | 441 g (2.27 moles) |
| 15 | Conc. H ₂ SO ₄ | 0.55 L |
| | Water | 1.63 L |
| | 50% NaOH | 1.27 L |

Procedure:

The reactor was charged with conc. H₂SO₄, and cooled to ~ 10°C. α -Phenyl- α -pyridyl-(2)-acetonitrile (from Example 1.A) was added portionwise, keeping the 20 temperature below 30°C. The reaction was stirred at ambient temperature for 16h. The reaction mixture then was cooled to 10°C, at which point water was added. The NaOH then was added to a pH of 12, keeping the temperature below 30°C. The resulting crystals were filtered, and the filter cake was washed with water and dried under vacuum to give 482 g 25 (100%) of α -phenyl- α -pyridyl-(2)-acetamide.

NH₄OH can be substituted for NaOH to adjust the pH to 12. One advantage of using NH₄OH is that the by-product that is formed (ammonium sulfate) is more soluble in water than the by-product (sodium sulfate) formed when NaOH is used as the base. Thus, the product crystals are less likely to be contaminated with inorganic salts.

5 **C. *d,l*-erythro- α -Phenyl- α -piperidyl-(2)-acetamide**

Materials:

| | | |
|----|---|---|
| | α -Phenyl- α -pyridyl-(2)-acetamide | 482 g (2.27 moles) |
| | Platinum oxide (PtO ₂) | 8.06 g |
| | Acetic acid | 1.68 + 4.13 L |
| 10 | Celite | 500 + 250 g |
| | Ethyl acetate | 3.10 + 0.62 + 2.07 + 2.07 + 4.13 + 0.21 L |
| | Water | 4.13 + 1.03 + 2.07 L |
| | 50% NaOH | 0.56 L |

Procedure:

15 The reactor was charged with α -phenyl- α -pyridyl-(2)-acetamide (from Example 1.B), acetic acid (1.68 L), and PtO₂. The reactor then was filled with hydrogen gas, and pressurized to 60 psi. The reaction mixture was hydrogenated at room temperature for 16h. The reaction mixture was filtered through a pad of Celite (500 g) to remove catalyst, and the Celite pad washed with acetic acid (4.13 L). The filtrate was concentrated under reduced
20 pressure. Ethyl acetate (3.10 L) was added to the residue and stirred for 2h. The resulting crystals (first crop) were filtered, washed with ethyl acetate (0.62 L), and dried. The filtrate was concentrated under reduced pressure. Ethyl acetate (2.07 L) was added to the residue and stirred for 2h. The resulting crystals (second crop) were filtered, washed with ethyl acetate (2.07 L), and dried. The crystals from first and second crops were combined and
25 dissolved in water (4.13 L), filtered through a pad of Celite (250 g), and the Celite pad was washed with water (1.03 L). The resulting filtrate was cooled to 10°C, followed by addition of 50% NaOH until the pH of the mixture was 13 and the free amine crystallized out. The

crystals were filtered, washed with water (2.07 L), and dried to give 297 g (60%) of *d,l*-*erythro*- α -phenyl- α -piperidyl-(2)-acetamide.

D. *l*-erythro- α -Phenyl- α -piperidyl-(2)-acetamide

Materials:

| | | |
|----|--|-----------------------|
| 5 | <i>d,l</i> -erythro- α -phenyl- α -piperidyl-(2)-acetamide | 297.2 g (1.361 moles) |
| | D-(-)-Tartaric acid | 204.3 g (1.361 moles) |
| | Methanol | 7.13 + 7.13 L |
| | Water | 2.0 L |
| 10 | 50% NaOH | 0.1 L |

Procedure:

D-(-)-Tartaric acid dissolved in methanol (7.13 L) was added to a stirred solution of *d,l*-erythro- α -phenyl- α -piperidyl-(2)-acetamide (from Example 1.C), dissolved in methanol (7.13 L). The resulting clear solution was stirred for 16h, whereby the tartrate salt of *l*-erythro-acetamide crystallized out. The crystals were filtered, washed with methanol and dried. This tartrate salt was dissolved in water and 50% NaOH was added to a pH of 12, whereby the free base precipitated out. The precipitated crystals were filtered, washed with water and dried to give 119 g (40%) of *l*-erythro- α -phenyl- α -piperidyl-(2)-acetamide.

E. *d*-threo- α -Phenyl- α -piperidyl-(2)-acetamide

20 Materials:

| | | |
|----|--|----------------------|
| | <i>l</i> -erythro- α -phenyl- α -piperidyl-(2)-acetamide | 119g (0.544 moles) |
| | Potassium t-butoxide (95%) | 141.5g (1.198 moles) |
| | Toluene | 3.57L |
| 25 | Water | 0.60 + 0.30 + 1.20L |
| | Conc. HCl | 0.24 + 0.12L |
| | 50% NaOH | 0.14L |

Procedure:

A mixture of 1-erythro- α -phenyl- α -piperidyl-(2)-acetamide (from Example 1.D), potassium t-butoxide, and toluene was heated to 70°C and stirred for 16h. The reaction mixture was cooled to room temperature, followed by slow addition of water (0.60L). Conc. HCl (0.24L) was added to this resulting mixture, and stirred for 0.5 h. The layers were separated, and the top organic layer was washed with a prepared solution of conc. HCl (0.12L) and water (0.30L). The combined aqueous layers were cooled to 10°C, and 50% NaOH was added to a pH of 12, whereby the free base precipitated out. The crystals were filtered, washed with water (1.20L), and dried to give 101 g (85%) of *d-threo*- α -phenyl- α -piperidyl-(2)-acetamide.

F. *d-threo*-Methylphenidate Hydrochloride

Materials:

| | | |
|----|--|-------------------------|
| | <i>d-threo</i> - α -phenyl- α -piperidyl-(2)-acetamide | 101 g (0.46 moles) |
| 15 | Conc. H ₂ SO ₄ | 121 mL |
| | Methanol | 1.1 L |
| | Water | 0.81 L |
| | 50% NaOH | 175 mL |
| | Diethyl ether | 1.0 + 1.0 + 1.0 + 1.0 L |
| 20 | Magnesium sulfate | 20 g |
| | HCl gas | As needed. |

Procedure:

A solution of *d-threo*- α -phenyl- α -piperidyl-(2)-acetamide (from Example 1.E) and conc. H₂SO₄ in methanol was heated to reflux and stirred for 2 days. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (0.81 L) and ether (1.0 L) were added to the residue. NaOH was added to a pH of 12, and the layers were separated. The aqueous layer was extracted with ether (1.0 L). MgSO₄ was added to the combined ether layers, filtered, and washed with ether (1.0 L). HCl gas was passed

through the filtrate with stirring, whereby white crystals of *d-threo*-methylphenidate hydrochloride precipitated out. The crystals were filtered, washed with ether (1.0 L), and dried to give 100 g (80%) of *d-threo*-methylphenidate hydrochloride.

The overall yield for Example 1 was 14.7%.

5 Example 2

Preparation of *d-Threo*-methylphenidate Hydrochloride Via Epimerization and Resolution of *d,l-Threo*-amide Enantiomers

A. α -Phenyl- α -pyridyl-2-acetonitrile

Materials:

| | | |
|----|------------------------|---------------------|
| 10 | 2-Chloropyridine (99%) | 172 g (1.50 moles) |
| | Benzyl cyanide (98%) | 188 g (1.576 moles) |
| | Sodium amide (90%) | 130 g (3.00 moles) |
| | Toluene | 0.59 + 0.10 L |
| | Water | 0.52 L |
| 15 | Ethyl acetate | 0.26 L |
| | Hexanes | 0.94 + 1.17 L |
| | Brine | 0.26 L |

Procedure:

The reactor was charged with 2-chloropyridine, benzyl cyanide, and toluene (0.59 L). Sodium amide powder was added over a 1h period via a solid-addition funnel, keeping the reaction temperature below 300°C. The reaction mixture was stirred for 16h at ambient temperature. The reaction was cooled to ~ 10°C, and quenched with 0.52 L water. Ethyl acetate (0.26 L) was added to solubilize the precipitated product.

The organic layer was separated and washed once with 0.26 L brine, and solvent was removed from the organic layer on a rotovap. Toluene (0.10 L), followed by hexanes (0.94 L) were added to the resulting residue. The resulting slurry was filtered, and the

filter cake was washed with hexanes (1.17 L), and dried to give 265 g of α -phenyl- α -pyridyl-(2)-acetonitrile as light brown crystals (90% yield based on 2-chloropyridine).

B. α -Phenyl- α -pyridyl-(2)-acetamide

Materials:

| | | |
|---|--|----------------------|
| 5 | α -Phenyl- α -pyridyl-(2)-acetonitrile | 264 g (1.362 moles) |
| | Conc. H ₂ SO ₄ | 0.33 L (6.226 moles) |
| | Water | 0.98 L |
| | 50% NaOH | 0.77 L |

Procedure:

- 10 The reactor was charged with conc. H₂SO₄, and cooled to $\sim 10^{\circ}\text{C}$. α -Phenyl- α -pyridyl-(2)-acetonitrile (from Example 2.A) was added portionwise, keeping the temperature below 30°C . The reaction was stirred at ambient temperature for 16h. The reaction mixture then was cooled to 10°C , the water was added, and the NaOH was added to a pH of 12, keeping the temperature below 30°C . The resulting crystals were
- 15 filtered, the filter cake was washed with water, and dried under vacuum to give 289 g (100%) of α -phenyl- α -pyridyl-(2)-acetamide.

C. *d,l*-erythro/threo- α -Phenyl- α -piperidyl-(2)-acetamide

Materials:

| | | |
|----|---|----------------------|
| 20 | α -Phenyl- α -pyridyl-(2)-acetamide | 289 g (1.365 moles) |
| | Platinum oxide (PtO ₂) | 4.84 g |
| | Acetic acid | 1.01 + 2.48 L |
| | Celite | 300 + 150 g |
| | Water | 2.48 + 0.62 + 1.24 L |
| | 50% NaOH | 0.33 L |

25 Procedure:

The reactor was charged with α -phenyl- α -pyridyl-(2)-acetamide (from Example 2.B), acetic acid (1.01 L), and PtO₂. The reactor then was filled with hydrogen gas, pressurized to 60 psi, and the mixture hydrogenated at room temperature for 16h. The

reaction mixture then was filtered through a pad of Celite (300 g) to remove the catalyst, and the Celite pad is washed with acetic acid (2.48 L). The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in water (2.48 L), filtered through a pad of Celite (150 g), and the Celite pad was washed with water (0.62 L). The
5 resulting filtrate was cooled to 10°C, followed by addition of 50% NaOH until the pH of the mixture was 13 and the free amine crystallized out. The crystals were filtered, washed with water (1.24 L), and dried to give 297 g (100%) of a 4:1 mixture of *d,l*-*erythro*- α -phenyl- α -piperidyl-(2)-acetamide and *d,l*-*threo*- α -phenyl- α -piperidyl-(2)-acetamide.

10 **D. *d,l*-*threo*- α -Phenyl- α -piperidyl-(2)-acetamide**

Materials:

| | | |
|----|---|----------------------|
| | Mixture of <i>d,l</i> - <i>erythro</i> -acetamide and <i>d,l</i> - <i>threo</i> -acetamide | 297 g (1.36 moles) |
| | Potassium t-butoxide (95%) | 354 g (2.996 moles) |
| 15 | Toluene | 8.92 L |
| | Water | 1.49 + 0.74 + 3.00 L |
| | Conc. HCl | 0.59 + 0.30 L |
| | 50% NaOH | 0.36 L |

Procedure:

20 A mixture of *d,l*-*erythro*-acetamide and *d,l*-*threo*-acetamide (from Example 2.C), potassium t-butoxide, and toluene was heated to 70°C and stirred for 16h. The reaction mixture was cooled to room temperature, followed by slow addition of water (1.49L). Conc. HCl (0.59L) was added to this resulting mixture, which was stirred for 0.5h. The layers were separated, and the top organic layer was then washed with a
25 prepared solution of conc. HCl (0.30L) and water (0.74L). The combined aqueous layers were cooled to 10°C, and 50% NaOH was added to a pH of 12 whereby the free base

precipitated out. The crystals were filtered, washed with water (3.00 L), and dried to give 253 g (85%) of *d,l-threo-α-phenyl-α-piperidyl-(2)-acetamide*.

E. *d-threo-α-Phenyl-α-piperidyl-(2)-acetamide*

Materials:

| | | |
|----|---|---------------------|
| 5 | <i>d,l-threo-α-phenyl-α-piperidyl-(2)-acetamide</i> | 253 g (1.159 moles) |
| | Dibenzoyl-D-tartaric acid | 415 g (1.159 moles) |
| | Isopropanol | 8.11 L |
| | 6N HCl (aqueous) | 1.67 L |
| 10 | Water | 1.0 L |
| | Solid NaCl | 290g |
| | 50% NaOH (aqueous) | 1.0 L |

Procedure:

Dibenzoyl-D-tartaric acid and *d,l-threo-α-phenyl-α-piperidyl-(2)-acetamide*

- 15 (from Example 2.D) were dissolved in isopropanol by warming the reaction mixture to ~50°C. The resulting clear solution was stirred at ambient temperature for 16h, whereby the tartrate salt of *d-threo-acetamide* crystallized out. The crystals were filtered, and the filter cake was washed with isopropanol and dried in a vacuum oven at 40°C. This tartrate salt was added in portions to a stirred solution of 6N aq. HCl, and the resultant
- 20 slurry was stirred at ambient temperature for 4h. The slurry was filtered, and the filter cake (containing free dibenzoyl-D-tartaric acid) was washed with water. Solid NaCl was added to the filtrate (which contained *d-threo-acetamide* hydrochloride salt) and the mixture was cooled to ~10°C. The NaOH was added to this mixture to a pH of 12, whereby the free base of *d-threo-acetamide* precipitated out. The precipitated crystals
- 25 were filtered, washed with water and dried to give 101 g (40%) of *d-threo-α-phenyl-α-piperidyl-(2)-acetamide*.

F. *d-threo*-Methylphenidate Hydrochloride

Materials:

| | | |
|----|---|-------------------------|
| | <i>d-threo</i> - α -phenyl- α -piperidyl-(2)- acetamide | 101 g (0.46 moles) |
| 5 | Conc. H ₂ SO ₄ | 121 mL |
| | Methanol | 1.1 L |
| | Water | 0.81 L |
| | 50% NaOH | 175 mL |
| | Diethyl ether | 1.0 + 1.0 + 1.0 + 1.0 L |
| 10 | Magnesium sulfate | 20 g |
| | HCl gas | As needed. |

Procedure:

A solution of *d-threo*- α -phenyl- α -piperidyl-(2)- acetamide (from Example 2.E) and conc. H₂SO₄ in methanol was heated to reflux and stirred for 2 days. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (0.81 L) and ether (1.0 L) were added to the residue. The NaOH was added to a pH of 12, and the layers were separated. The aqueous layer was extracted with ether (1.0 L). MgSO₄ was added to the combined ether layers, filtered, and washed with ether (1.0 L). HCl gas was passed through the filtrate with stirring, whereby white crystals of *d-threo*-methylphenidate hydrochloride precipitated out. The crystals were filtered, washed with ether (1.0 L), and dried to give 100 g (80%) of *d-threo*-methylphenidate hydrochloride.

In contrast to Example 1, the overall yield for Example 2 was 24.5%, an increase of over 66%.

Example 3

Preparation of *l*-Threo-methylphenidate Hydrochloride *Via* Epimerization and Resolution of *d,l*-Threo-amide Enantiomers

A. α -Phenyl- α -pyridyl-2-acetonitrile

5 Materials:

| | | |
|----|------------------------|---------------------|
| | 2-Chloropyridine (99%) | 172 g (1.50 moles) |
| | Benzyl cyanide (98%) | 188 g (1.576 moles) |
| | Sodium amide (90%) | 130 g (3.00 moles) |
| | Toluene | 0.59 + 0.10 L |
| 10 | Water | 0.52 L |
| | Ethyl acetate | 0.26 L |
| | Hexanes | 0.94 + 1.17 L |
| | Brine | 0.26 L |

Procedure:

15 The reactor was charged with 2-chloropyridine, benzyl cyanide, and toluene (0.59 L). Sodium amide powder was added over a 1h period via a solid-addition funnel, keeping the reaction temperature below 300°C. The reaction mixture was stirred for 16h at ambient temperature. The reaction was cooled to ~ 10°C, and quenched with 0.52 L water. Ethyl acetate (0.26 L) was added to solubilize the precipitated product.

20 The organic layer was separated and washed once with 0.26 L brine, and solvent was removed from the organic layer on a rotovap. Toluene (0.10 L), followed by hexanes (0.94 L) were added to the resulting residue. The resulting slurry was filtered, and the filter cake was washed with hexanes (1.17 L), and dried to give 265 g of α -phenyl- α -pyridyl-(2)-acetonitrile as light brown crystals (90% yield based on 2-chloropyridine).

25 B. α -Phenyl- α -pyridyl-(2)-acetamide

Materials:

| | | |
|----|--|----------------------|
| | α -Phenyl- α -pyridyl-(2)-acetonitrile | 264 g (1.362 moles) |
| | Conc. H ₂ SO ₄ | 0.33 L (6.226 moles) |
| | Water | 0.98 L |
| 30 | 50% NaOH | 0.77 L |

Procedure:

The reactor was charged with conc. H_2SO_4 , and cooled to $\sim 10^\circ\text{C}$. α -Phenyl- α -pyridyl-(2)-acetonitrile (from Example 3.A) was added portionwise, keeping the temperature below 30°C . The reaction was stirred at ambient temperature for 16h. The reaction mixture then was cooled to 10°C , the water was added, and the NaOH was added to a pH of 12, keeping the temperature below 30°C . The resulting crystals were filtered, the filter cake was washed with water, and dried under vacuum to give 289 g (100%) of α -phenyl- α -pyridyl-(2)-acetamide.

C. *d,l*-erythro/threo- α -Phenyl- α -piperidyl-(2)-acetamide

10 Materials:

| | | |
|----|---|----------------------|
| | α -Phenyl- α -pyridyl-(2)-acetamide | 289 g (1.365 moles) |
| | Platinum oxide (PtO_2) | 4.84 g |
| | Acetic acid | 1.01 + 2.48 L |
| | Celite | 300 + 150 g |
| 15 | Water | 2.48 + 0.62 + 1.24 L |
| | 50% NaOH | 0.33 L |

Procedure:

The reactor was charged with α -phenyl- α -pyridyl-(2)-acetamide (from Example 3.B), acetic acid (1.01 L), and PtO_2 . The reactor then was filled with hydrogen gas, pressurized to 60 psi, and the mixture hydrogenated at room temperature for 16h. The reaction mixture then was filtered through a pad of Celite (300 g) to remove the catalyst, and the Celite pad is washed with acetic acid (2.48 L). The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in water (2.48 L), filtered through a pad of Celite (150 g), and the Celite pad was washed with water (0.62 L). The resulting filtrate was cooled to 10°C , followed by addition of 50% NaOH until the pH of the mixture was 13 and the free amine crystallized out. The crystals were filtered, washed with water (1.24 L), and dried to give 297 g (100%) of a 4:1 mixture of *d,l*-

erythro- α -phenyl- α -piperidyl-(2)-acetamide and *d,l-threo*- α -phenyl- α -piperidyl-(2)-acetamide.

D. *d,l-threo*- α -Phenyl- α -piperidyl-(2)-acetamide

Materials:

| | | |
|----|--|----------------------|
| 5 | Mixture of <i>d,l-erythro</i> -acetamide and <i>d,l-threo</i> -acetamide | 297 g (1.36 moles) |
| | Potassium t-butoxide (95%) | 354 g (2.996 moles) |
| | Toluene | 8.92 L |
| | Water | 1.49 + 0.74 + 3.00 L |
| 10 | Conc. HCl | 0.59 + 0.30 L |
| | 50% NaOH | 0.36 L |

Procedure:

A mixture of *d,l-erythro*-acetamide and *d,l-threo*-acetamide (from Example 3.C), potassium t-butoxide, and toluene was heated to 70°C and stirred for 16h. The reaction mixture was cooled to room temperature, followed by slow addition of water (1.49L). Conc. HCl (0.59L) was added to this resulting mixture, which was stirred for 0.5h. The layers were separated, and the top organic layer was then washed with a prepared solution of conc. HCl (0.30L) and water (0.74L). The combined aqueous layers were cooled to 10°C, and 50% NaOH was added to a pH of 12 whereby the free base precipitated out. The crystals were filtered, washed with water (3.00 L), and dried to give 253 g (85%) of *d,l-threo*- α -phenyl- α -piperidyl-(2)-acetamide.

E. *l-threo*- α -Phenyl- α -piperidyl-(2)-acetamide

Materials:

| | | |
|----|---|----------------------|
| 25 | <i>d,l-threo</i> - α -phenyl- α -piperidyl-(2)- acetamide | 253 g (1. 159 moles) |
| | Dibenzoyl-L-tartaric acid | 415 g (1. 159 moles) |
| | Isopropanol | 8.11 L |
| | 6N HCl (aqueous) | 1.67 L |
| | Water | 1.0 L |
| 30 | Solid NaCl | 290g |
| | 50% NaOH (aqueous) | 1.0 L |

Procedure:

Dibenzoyl-L-tartaric acid and *d,l*-threo- α -phenyl- α -piperidyl-(2)-acetamide (from Example 3.D) is dissolved in isopropanol by warming the reaction mixture to ~ 50°C. The resulting clear solution is stirred at ambient temperature for 16h, whereby the

5 tartrate salt of *l*-threo-acetamide crystallizes out. The crystals are filtered, and the filter cake washed with isopropanol and dried in a vacuum oven at 40°C. This tartrate salt is added in portions to a stirred solution of 6N aq. HCl, and the resultant slurry is stirred at ambient temperature for 4h. The slurry is filtered, and the filter cake (containing free dibenzoyl-L-tartaric acid) is washed with water. Solid NaCl is added to the filtrate

10 (which contains *l*-threo-acetamide hydrochloride salt) and the mixture is cooled to ~10°C. The NaOH is added to this mixture to a pH of 12, whereby the free base of *l*-threo-acetamide precipitates out. The precipitated crystals are filtered, washed with water and dried to give *l*-threo- α -phenyl- α -piperidyl-(2)- acetamide.

F. *l*-threo-Methylphenidate Hydrochloride

15 Materials:

| | | |
|----|---|-------------------------|
| | <i>l</i> -threo- α -phenyl- α -piperidyl-(2)- acetamide | 101 g (0.46 moles) |
| | Conc. H ₂ SO ₄ | 121 mL |
| | Methanol | 1.1 L |
| 20 | Water | 0.81 L |
| | 50% NaOH | 175 mL |
| | Diethyl ether | 1.0 + 1.0 + 1.0 + 1.0 L |
| | Magnesium sulfate | 20 g |
| | HCl gas | As needed. |

25 Procedure:

A solution of *l*-threo- α -phenyl- α -piperidyl-(2)- acetamide (from Example 3.E) and conc. H₂SO₄ in methanol is heated to reflux and stirred for 2 days. The reaction mixture is cooled to room temperature and concentrated under reduced pressure. Water

(0.81 L) and ether (1.0 L) are added to the residue. The NaOH is added to a pH of 12, and the layers are separated. The aqueous layer is extracted with ether (1.0 L). MgSO_4 is added to the combined ether layers, filtered, and washed with ether (1.0 L). HCl gas is passed through the filtrate with stirring, whereby white crystals of *l-threo*--

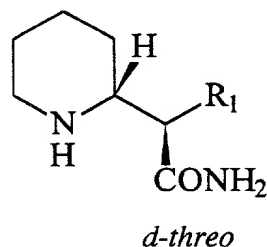
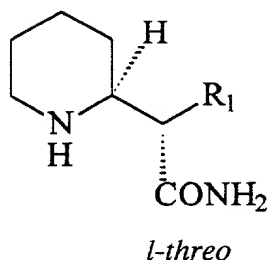
- 5 methylphenidate hydrochloride precipitate out. The crystals are filtered, washed with ether (1.0 L), and dried to give *l-threo*-methylphenidate hydrochloride.

Those skilled in the art will appreciate that numerous changes and modifications may be made to the preferred embodiments of the present invention and that such changes and modifications may be made without departing from the spirit of
10 the invention. It is therefore intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

Approved for Release by NSA on 09-10-2013 pursuant to E.O. 13526

WHAT IS CLAIMED IS:

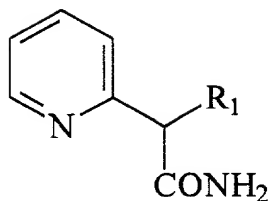
1. A synthetic process comprising the steps of:
providing *d,l-threo* piperidyl acetamide stereoisomers having formulas:



- 5
wherein R₁ is aryl having about 6 to about 28 carbon atoms; and
reacting said stereoisomers with an acid resolving agent in an organic solvent,
thereby forming acid salts of said *d-threo* stereoisomers preferentially with respect to
said *l-threo* stereoisomers.

- 10
2. The process of claim 1 wherein R₁ phenyl.
3. The process of claim 1 wherein said solvent comprises an alcohol, an
alkyl alkanoate, a ketone, or an ether.
4. The process of claim 1 wherein said solvent is an alkyl alcohol having 1
to about 5 carbon atoms.
- 15
5. The process of claim 1 wherein said alkyl alcohol is isopropanol.

6. The process of claim 1 wherein said acid resolving agent is a derivative of D-tartaric acid.
7. The process of claim 1 wherein said acid resolving agent is a tartaric acid derivative having formula $\text{HO}_2\text{CCH}[\text{OC}(\text{O})\text{R}_3]\text{CH}[\text{OC}(\text{O})\text{R}_3]\text{CO}_2\text{H}$ wherein each
- 5 R_3 , independently, is aryl having 6 to about 28 carbon atoms or aralkyl having 7 to about 28 carbon atoms.
8. The process of claim 7 wherein R_3 is aralkyl having 7 to about 28 carbon atoms.
9. The process of claim 6 wherein said acid resolving agent is dibenzoyl-
- 10 D-tartaric acid.
10. The process of claim 1 further comprising reacting said *d-threo* acid salts with aqueous base to form said *d-threo* piperidine acetamide.
11. The process of claim 10 further comprising reacting said *d-threo*
- 15 piperidine acetamide with an alcohol having 1 to about 5 carbon atoms in the presence of acid to form a *d-threo* piperidine acetate.
12. The process of claim 1 wherein said *d,l-threo* piperidyl acetamide stereoisomers are prepared by reacting a pyridine having formula:



with hydrogen in an alkanolic acid having 1 to about 10 carbon atoms in the presence of a catalyst to provide a mixture of *threo* and *erythro* piperidyl stereoisomers; and

contacting said *erythro* stereoisomers with organic base, thereby converting

5 said *erythro* piperidyl stereoisomers to *threo* piperidyl stereoisomers.

13. The product of the process of claim 1.

14. The product of the process of claim 10.

ABSTRACT OF THE DISCLOSURE

Processes and intermediates for preparing 2-substituted piperidines such as 2-substituted *d-threo* piperidines are provided, including processes and intermediates for resolution of piperidyl acetamide stereoisomers.

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and

I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **PROCESSES AND INTERMEDIATES FOR RESOLVING PIPERIDYL ACETAMIDE STEREOISOMERS** the specification of which:

() is attached hereto.

(XX) was filed on May 22, 197 as Application Serial No. 08/861,988 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to the patentability of this application in accordance with 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a-d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of any application on which priority is claimed:

| Country | Number | Date Filed | Priority Claimed | | | |
|---------|--------|------------|------------------|--|----|--|
| | | | Yes | | No | |
| | | | Yes | | No | |

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge

the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

| Application Serial No. | Filing Date | Status (pending, patented) |
|------------------------|-------------|----------------------------|
| | | |
| | | |
| | | |

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

| Provisional Application No. | Filing Date |
|-----------------------------|-------------|
| | |
| | |

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: **John W. Caldwell and Joseph Lucci**, Registration Nos. 28,937 and 33,307 of the firm of **WOODCOCK WASHBURN KURTZ MACKIEWICZ & NORRIS LLP**, One Liberty Place - 46th Floor, Philadelphia, Pennsylvania 19103, and

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Joseph Lucci, Esq.
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One Liberty Place - 46th Floor
Philadelphia, PA 19103
Telephone No. 215-568-3100.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| | | | |
|---|--|--|--------------------------|
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| | Post Office Address: | | |